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HIGHLY DISPERSED POTASSIUM ON ALUMINA AS A METALATING AGENT. ALKYLATION OF ENOLIZABLE COMPOUNDS

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Summary

Highly dispersed potassium on alumina (K/Al_2O_3) acts as a metalating agent towards enolizable compounds and the intermediate organopotassium derivatives can be alkylated with primary alkyl bromides. The reaction conditions are dependent on the substrate. In particular, tetrahydrofuran is the solvent of choice for the metalation of nitriles and aldehyde *N,N*-dimethylhydrazones at —60°C and of *N*-cyclohexyl ketimines at room temperature, whereas hexane must be used for ketones.

Introduction

In the developments of new synthetic techniques, increasing attention has been paid in the last few years to solid-phase synthesis [1]. Heterogeneous reactions effected by reagents immobilized on porous solids are very useful in organic synthesis, often being more selective than the corresponding homogeneous reactions. Moreover they are simple to perform, since product isolation involves only filtration and solvent evaporation.

Particular emphasis has been placed on the use of alumina in heterogeneous organic reactions, such as Oppenauer-type oxidations and Meerwein—Ponndorf—Verley-type reductions [2], intramolecular cyclizations [2,3], malonic ester synthesis [4], and nucleophilic substitutions by impregnated alkali metal salts [2,5]. Furthermore, alkali metals dispersed on alumina are active catalysts for the isomerization of alkenes and the partial hydrogenation of open-chain and cyclic alkadienes [6].

We recently reported that highly dispersed potassium on alumina (K/Al_2O_3) can reductively eliminate the cyano group from alkyl nitriles in hexane solution at room temperature to give the corresponding hydrocarbons [7] (eq. 1).

$$R{-}CN \xrightarrow[\text{hexane}]{K/Al_2O_3} R{-}H \qquad (1)$$

We now report that K/Al_2O_3 can be used as a metalating agent for enolizable compounds; behaviour analogous to that of potassium graphite (C_8K) [8] and of alkali metals dispersed on charcoal [9].

Results and discussion

Alkyl nitriles, esters, ketones, *N*-cyclohexyl ketimines and aldehyde *N,N*-dimethylhydrazones underwent α-metalation with hydrogen evolution upon treatment with K/Al_2O_3. The intermediate carbanion could then be trapped with an alkyl bromide.

All the reactions were performed on 10 mmol of enolizable substrate using 25 mmol of potassium dispersed on alumina (17% potassium loading by weight) The excess of potassium was necessary to increase the efficiency of the metalation, and thus at least a 50% excess of alkyl bromide was used in the alkylation step to allow for concomitant reduction and Wurtz coupling of the halide.

Selected examples of alkylation reactions are described in detail below, substrates requiring the same experimental procedure being examined together.

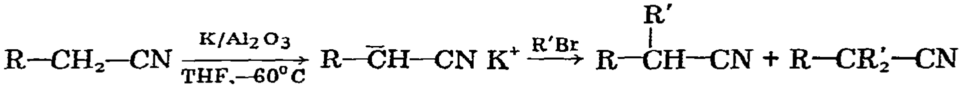
Alkylation of nitriles and butanal N,N-dimethylhydrazone (Procedure A)

Alkyl nitriles (I) were metalated by addition to a slurry of K/Al_2O_3 in tetrahydrofuran at —60° C, and the intermediate potassium salts (II) were alkylated with a primary alkyl bromide (Scheme 1). The monoalkylated products (III) were generally accompanied by a small amount of the corresponding dialkylated products (IV).

The reductive decyanation of nitriles, which is the prevalent reaction when hexane is used as solvent (eq. 1), also occurred to a considerable extent in THF, as demonstrated by the isolation of 2-(hexyl-1-oxy)tetrahydro-2*H*-pyran in 41% yield from the nitrile Ic. No attempt was made to detect the formation of methane and propane from Ia and Ib, respectively.

The alkylation of butanal *N,N*-dimethylhydrazone (V) was also performed in THF at —60° C (Scheme 2). In addition to the monoalkylated product VI (44% yield), a small amount of the aldehyde VIII (5% yield) was obtained by alkaline hydrolysis of the hydrazonium ion VII coming from *N*-alkylation of VI [10].

SCHEME 1.

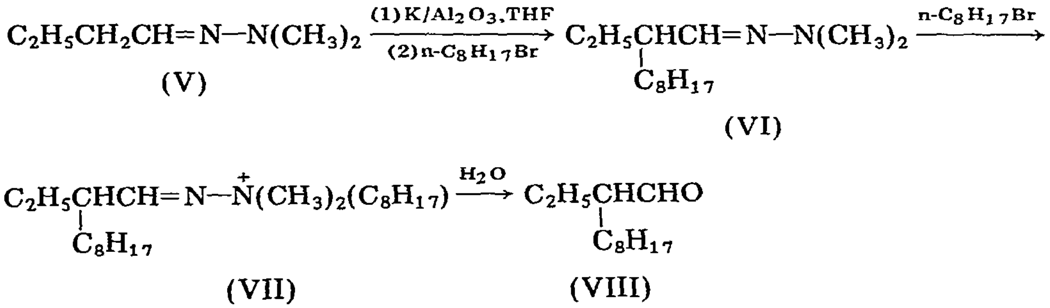


$$R{-}CH_2{-}CN \xrightarrow[THF,-60^\circ C]{K/Al_2O_3} R{-}\bar{C}H{-}CN\ K^+ \xrightarrow{R'Br} R{-}\overset{R'}{\overset{|}{C}}H{-}CN + R{-}CR'_2{-}CN$$

(I)	(II)	(III)(%)	(IV)(%)
Ia, R = H;	a, R' = n-C_8H_{17}	54	3
Ib, R = C_2H_5;	b, R' = n-C_8H_{17}	55	3
Ic, R = THPO$(CH_2)_5$ *	c, R' = n-C_6H_{13}	48	0

* THP is tetrahydropyranyl.

SCHEME 2



$$C_2H_5CH_2CH{=}N{-}N(CH_3)_2 \xrightarrow[(2)\,n\text{-}C_8H_{17}Br]{(1)\,K/Al_2O_3,THF} C_2H_5\underset{\displaystyle C_8H_{17}}{\underset{|}{C}}HCH{=}N{-}N(CH_3)_2 \xrightarrow{n\text{-}C_8H_{17}Br}$$
$$\text{(V)} \qquad\qquad\qquad\qquad \text{(VI)}$$

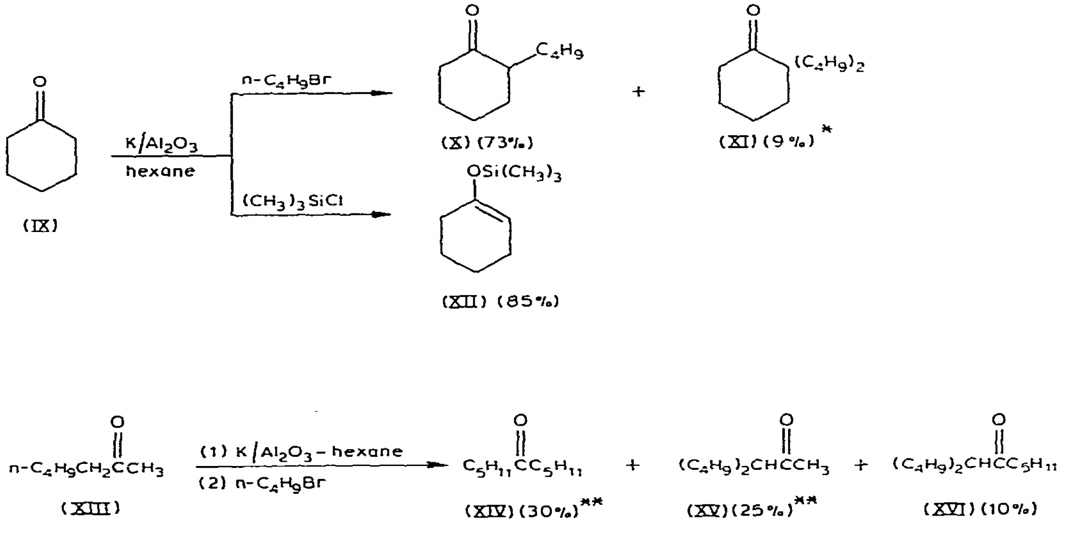
$$C_2H_5\underset{\displaystyle C_8H_{17}}{\underset{|}{C}}HCH{=}N{-}\overset{+}{N}(CH_3)_2(C_8H_{17}) \xrightarrow{H_2O} C_2H_5\underset{\displaystyle C_8H_{17}}{\underset{|}{C}}HCHO$$
$$\text{(VII)} \qquad\qquad\qquad\qquad \text{(VIII)}$$

When the reaction was carried out in hexane, following Procedure B, nitriles and hydrocarbons were also obtained. We believe that, as observed by Normant [11] using lithium dialkylamides in benzene/hexamethylphosphoric triamide, the α-branched hydrazone VI may be metalated at the azomethyne group to give, after elimination of potassium dimethylamide, 2-ethyl decanenitrile (IIIb). The latter would then undergo decyanation to undecane, and further alkylation and decyanation reactions.

Alkylation of ketones and esters (Procedure B)

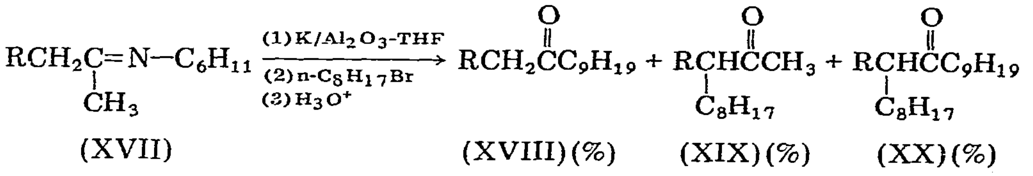
Ketones were effectively alkylated in hexane at room temperature, whereas in THF a complex mixture of alkylation and reduction products was obtained. In the case of cyclohexanone (IX), the monoalkylated (X) predominated over the dialkylated products (XI) (Scheme 3). Interestingly, the silyl enol ether (XII) was readily prepared by this method in 85% yield. Unsymmetrical ketones afforded the two isomeric α- and α′-alkylated derivatives in approximately the same yield, as reported for 2-heptanone (XIII).

SCHEME 3.



* Mixture of α,α′-isomers. ** The regioisomers were not separated; the relative amounts were evaluated from the GLC peak areas.

SCHEME 4



$$RCH_2\underset{CH_3}{\underset{|}{C}}{=}N{-}C_6H_{11} \xrightarrow[\substack{(2)\,n\text{-}C_8H_{17}Br\\(3)\,H_3O^+}]{(1)\,K/Al_2O_3\text{-THF}} RCH_2\overset{O}{\overset{\|}{C}}C_9H_{19} + R\underset{C_8H_{17}}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}CH_3 + R\underset{C_8H_{17}}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}C_9H_{19}$$

(XVII)

	(XVIII)(%)	(XIX)(%)	(XX)(%)
a, R = H	41		20
b, R = CH_3	63 *(45)**	7 *(4)**	

* The regioisomers were not separated; the relative ratio was evaluated from the GLC peak areas. ** The reaction was performed in hexane, according to Procedure B.

Among the esters, ethyl phenylacetate was alkylated by the same procedure with 1-bromobutane to give ethyl 2-phenylhexanoate in 69% yield, together with ethyl 2-butyl-2-phenylhexanoate (3%). However, ethyl butanoate always gave only 15% or less of the monoalkylated product regardless of solvent and temperature, because of extensive condensation reactions.

Alkylation of N-cyclohexyl ketimines (Procedure C)

Alkylation of aliphatic *N*-cyclohexyl ketimines was best performed in THF at room temperature. Acidic hydrolysis of the reaction mixtures afforded the corresponding alkylated ketones in satisfactory overall yields (Scheme 4). The α,α'-dialkylated ketone (XX) was obtained in considerable amount from the symmetrical imine XVIIa even when equimolar amounts of potassium, imine and alkyl bromide were used. A remarkable regioselective alkylation at the less substituted site was observed on the unsymmetrical ketimine XVIIb, both in THF and in hexane. In hexane, however, yields were somewhat lower.

Experimental

Materials

Activated neutral alumina (Brockmann activity I, 70—230 mesh ASTM) was purchased from Merck. Potassium (RPE, 99.5%) was obtained from Carlo Erba, as was acetonitrile and cyclohexane. Butanenitrile, 2-heptanone and ethyl phenylacetate were from Fluka. *N*-2-Propylidene cyclohexylamine (XVIIa) [8b], *N*-2-butylidene cyclohexylamine (XVIIb) [8b], 7-[(tetrahydro-2 H-pyran-2-yl)oxy]-heptanenitrile (Ic) [7] and butanal *N,N*-dimethylhydrazone (V) [12] were prepared by known methods.

Solvents

Tetrahydrofuran (THF) was distilled over sodium benzophenone ketyl under argon. Hexane (isomer mixture, b.p. 65—70° C) was distilled and stored over sodium in an inert atmosphere.

Products

All compounds were characterized by IR, NMR and MS spectra or by comparison with authentic samples. Reported yields refer to pure compounds isolated by distillation or chromatography.

Analyses

IR spectra were obtained on a Perkin—Elmer 710B spectrophotometer. ^1H NMR spectra were recorded at 60 MHz on a Perkin—Elmer R12B spectrometer using tetrachloromethane as solvent; chemical shifts are expressed as δ in ppm from tetramethylsilane. Mass spectra (MS) were taken on a Varian MAT 111 instrument at 70 eV. Gas chromatographic analyses were carried out on a Hewlett—Packard 5750B apparatus using a 2 m × 2 mm column packed with 5% SF96 on silanized Chromosorb G (80—100 mesh). Column chromatography was performed on silica gel (Merck, 230—400 mesh ASTM) using hexane ether mixtures as eluent.

Preparation of highly dispersed potassium on alumina (K/Al_2O_3)

Al_2O_3 (5.0 g) was placed in a 100 ml two-necked flask equipped with an argon inlet and a magnetic stirring bar and heated at 130°C (external oil bath) for 15 min under a positive argon pressure. Then potassium (1.0 g, 25 mmol) was added in small pieces. After the potassium melted the heating was stopped and the mixture was vigorously stirred to obtain a homogeneous black powder of highly dispersed metal (17% potassium loading by weight). K/Al_2O_3 is oxygen and moisture sensitive, but is stable for several days in an inert atmosphere.

General procedures for the alkylation reactions

Procedure A: alkylation of 7-[(tetrahydro-2 H-pyran-2-yl)oxy]heptanenitrile (Ic). A solution of the nitrile Ic (2.1 g, 10 mmol) in anhydrous THF (10 ml) was added dropwise to a slurry of K/Al_2O_3 (6.0 g, 17% of K, 25 mmol) in THF (15 ml) at —60°C, and the mixture was stirred for 3 h at the same temperature. 1-Bromohexane (2.5 g, 15 mmol) dissolved in THF (5 ml) was then added and the stirring was continued for 3 h at —60°C. The reaction was then quenched with water (5 ml) and the solution filtered. The organic phase was dried (Na_2SO_4) and evaporated. Column chromatography (hexane/ether 99/1) of the crude residue afforded 2-(hexyl-1-oxy)tetrahydro-2 H-pyran [7] (0.76 g, 41%), b.p. 110°C/15 Torr; IR (neat) 1130, 1110, 1070, 1030 cm^{-1}; NMR 4.6 (m, 1 H), 3.5 (m, 4 H), 1.4—1.8 (14 H), 0.95 (t, 3 H). By eluting with hexane/ether 97/3 it was possible to isolate 2-[5-[(tetrahydro-2 H-pyran-2-yl)pentyl]octanenitrile (IIIc) (1.41 g, 48%); IR (neat) 2240, 1140, 1070, 1030 cm^{-1}; NMR 4.5 (m, 1 H), 3.5 (m, 4 H), 2.4 (m, 1 H), 1.5 (m, 24 H), 0.95 (t, 3 H).

Procedure B: alkylation of cyclohexanone. A solution of cyclohexanone (1.0 g, 10 mmol) in hexane (10 ml) was added dropwise to a slurry of K/Al_2O_3 (6.0 g. 17% of K, 25 mmol) in hexane (15 ml) at room temperature with stirring. After 3 h a solution of trimethylchlorosilane (1.7 g, 15 mmol) in hexane (5 ml) was added and the stirring was continued for 3 h at room temperature. The reaction was then quenched with water (5 ml) and filtered. The organic phase was dried (Na_2SO_4) and concentrated. The residue was distilled to give (1-cyclohexen-1-yloxy)trimethylsilane (XII) (1.44 g, 85%), b.p. 78—80°C/25 Torr (lit. [13]: 74—75°C/20 Torr); IR (neat) 3030, 1660, 1250, 1190, 890, 840; NMR 4.7 (m, 1 H), 1.9 (m, 4 H), 1.55 (m, 4 H), 0.1 (s, 9 H); MS m/e 170 (M^+).

Procedure C: alkylation of N-2-propylidene cyclohexylamine (XVIIa). A solution of the imine (1.39 g, 10 mmol) in anhydrous THF (10 ml) was added dropwise with stirring at room temperature to a slurry of K/Al_2O_3 (6.0 g, 17%

of K, 25 mmol) in THF (15 ml). After 3 h a solution of 1-bromooctane (2.9 g, 15 mmol) in THF (10 ml) was added and stirring was continued for 3 h. Then the reaction was quenched with water (5 ml) and filtered. The organic phase was stirred with 5% aqueous oxalic acid (30 ml) for 1 h, then extracted with ether and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on a silica gel column. Elution with hexane afforded 10-nonadecanone (XXa, 0.42 g, 20% yield based on alkyl halide), m.p. 59°C (lit. [14]: 58°C); IR (Nujol mull): 1710; NMR 2.3 (t, 4 H), 1.3 (28 H), 0.95 (t, 6 H). Successive elution with hexane/ether 97/3 gave 2-undecanone (XVIIIa) (0.70 g, 41%), b.p. 109—111°C/18 Torr (lit. [15]: 112°C/17 Torr); IR (neat): 1715; NMR 2.4 (t, 2 H), 2.05 (s, 3 H), 1.3 (14 H), 0.95 (t, 3 H); MS *m/e* 170 (M^+).

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